REMARKS

Claims 1-39 are pending in this application. Claims 1-3, 12-14, 16-17, 23-36 and 39 are amended herein. New claim 40 is added herein. With entry of this amendment claims 1-39 are under consideration. No new matter is introduced by way of the amendments to the specification or claims.

Applicant amends the specification and claims herein as requested to conform the spelling of certain words to the Examiner's preferred American usage and to conform the the claims to the common American format. Claims 1, 2, 16, 17, 24-34 and 39 have been amended to clarify antecedent basis.

Support for the amendments to the claims is found throughout the specification and claims as originally filed. For example, support for forming a viscous liquid from a preservation sample under pressure conditions of at least 2 mBars is found, *e.g.*, on page 11, line 17 of the instant specification. Support for forming the viscous liquid under pressure conditions of less than 20 mBars is found, *e.g.*, on page 11, line 11 of the instant specification. Support for a composition including a highly viscous liquid containing an active agent and a glass forming polyol stabilizing agent as in claim 23, is found, for example, on pages 4-6 and in the Examples of the instant specification. Literal support for highly viscous liquids having less than 15% solvent (w/w) is found, *e.g.*, on page 5, line 18 of the instant specification. Express support for polyl stabilizing agents is found, *e.g.*, on page 6, lines 6-16 of the instant specification. Support for compositions and methods of drying (by evaporation) for producing compositions containing an active agent that retain at least 40% of activity, antigenicity and/or immunogenicity as compared to a reference sample that has not been subject to the drying (evaporation) process as in claims 1 and 23, is found, for example, on page 17, line 26, and in the Examples of the instant specification.

IN THE SPECIFICATION

The Examiner objects to certain informalities in the Specification. Applicant amends the specification herein in accordance with the Examiner's instructions. For example, Applicant amends the spelling of certain words (*e.g.*, stabilising, lyophilised)

according to common British English usage to reflect common American English usage (stabilizing, lyophilized).

The Examiner also notes that: "throughout the specification, there are references to "step b", "step c", *e.g.*, page 13, line 31. However there is no recitation of a "step a"." Applicant herein amends the first paragraph of the Detailed Description, beginning on page 4, line 10 of the instant specification, to replace bullet point indicators with the letter indicators a), b) and c). Applicant also notes that claims 1 and 2 have been amended to reflect the same letter indicators, which were inadvertently removed during the preparation of the preliminary amendment filed April 29, 2005.

IN THE CLAIMS

Claim Objections

As noted above, Applicant herein amends the claims according to the Examiner's instructions to conform the spelling of certain terms to the Examiner's preferred American English usage.

Claim Rejections – 35 U.S.C. § 112

Claims 1-22 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant herein amends claim 1 to clarify that "the" active agent dissolved or suspended in a solution of a stabilizing agent in step (a) is the same active agent referenced in the preamble. Applicant believes that this amendment clarifies antecedent basis of the active agent and renders the rejection of claims 1-22 moot.

Claims 3-11 also stand rejected under 35 U.S.C. § 112, second paragraph, because the claims recite the limitations "step (b)" and "step (c)" and claim 1 from which claims 3-11 depend does not recite any steps labeled "a", "b", or "c". Applicant herein amends claims 1 and 2 to indicate the appropriate steps by letter indicators a), b) and c), rendering the rejection moot.

Claims 23-39 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action contends that claims 23-39 are unclear are because "[t]he metes and bounds of what constitutes a 'highly' viscous liquid versus a viscous liquid is unclear." Applicant herein amends claim 23 to clarify that the claimed composition is a highly viscous liquid, which "comprises a solvent content of less than 15% (w/w)." In view of the amendments to claim 23, Applicant believes that the rejection is rendered moot.

Claims 26-39 also stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because it is allegedly "unclear if claims 24-39 are only claiming the liquid, or the highly viscous liquid composition comprising an active agent." As recommended by Examiner, Applicant herein amends claim 23 to clarify that it is the "composition" including a highly viscous liquid comprising an active agent that is the subject matter of claims 23-39.

Claim 3 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite because the claim is drawn to a method of preserving an active agent under conditions that do not result in "freezing or bubbling involved in foam formation." To facilitate understanding, Applicant herein amends claim 3 has been amended to expressly recite conditions that do not result in freezing or bubbling. More specifically, Applicant amends claim 3 to indicate that the evaporation is performed at pressure of "at least 2 mBars and no more than 20 mBars during step b)."

Claims 23-39 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite on the grounds that because "all of the experiments presented in the specification appear to show that there is loss of activity no matter what the conditions," it is "unclear how antigenicity or activity of the active agent is preserved." Applicant herein amends claim 24 to include a numerical definition of antigenicity and/or activity preservation as disclosed in the Detailed Description on page 17, *e.g.*, at lines 26-27 of the instant specification. Applicant believes that this amendment renders the rejection moot.

Claims 1-39 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action states:

> The claims are drawn to a method of preservation or a composition comprising a highly viscous liquid and an active agent, wherein a stabilizing agent is chosen from a group of glass forming polyols and utilized at a variety of concentrations. However, the specification teaches only sucrose and trehalose as the polyol, and that any concentration less than 10% resulted in 100% loss of activity of the active agent (Table 2). It is unclear how any concentration of sucrose or trehalose less than 10% preserves the activity of the active agent.

To the extent that the Examiner maintains the rejection with respect to the amended claims, Applicant traverses. The specification teaches that suitable stabilizing agents include glass forming polyols. The instant specification provides a list of suitable examples is provided, for example, on page 6, lines 11-15. Two specific examples of suitable stabilizing agents are sucrose and trehalose, which are used for illustrative purposes in the Examples. Nonetheless, one of ordinary skill in the art at the time the application was filed would have been aware that any polyol (or other stabilizing agent) capable of forming a "glass" in concentrated aqueous solution (as opposed to separating from the solvent into crystals) is suitable as a stabilizing agent. As of the filing date of this application, glass forming polyols were well known in the pharmaceutical industry for their stabilizing properties in the context of drying (*e.g.*, freeze drying and air drying). For example, as stated in a review article by Franks published in 2003:

> The technological potential of vitreous aqueous solutions was first recognized during themoanalytical studies of freeze-drying and air drying. In the pharmaceutical industry it had long been known that the stability of drugs, especially those based on proteins, was considerably enhanced by freeze-drying, but that this process required the addition of so-called 'excipients' to the solution to be dried. Empirical approaches had suggested that carbohydrates were particularly effective in providing enhanced drug stability.
>
> Franks, *Biophysical Chem.* 105:251-261, 2003, p. 254 (*see*, second paragraph under heading "3. Aqueous solid solutions.")

Franks later discusses common properties of "polyhydroxy compounds" (a group that includes polyols that provide stabilizing benefits during and after the drying of labile biomaterials. Importantly, these stabilizing agents exhibit "a reluctance to crystallize

from aqueous solution." (Franks, p. 256, column 1, lines 4-7). Further, "[i]t is the resulting tendency to supersaturation that produces the vitrification of pharmaceutical preparations, and helps to confer an improved degree of stability on such products." (Franks, p. 256, column 1, lines 17-20). Franks provides the following list of exemplary polyhydroxy compounds: glycerol, ribose, xylose, arabinose, fructose, glucose, mannitol, sorbiotol, sucrose, trehalose, maltose, raffinose, maltotriose and stachyose. (Franks, p. 256, Table 2). Thus, at the time the application was filed, one of skill in the art would clearly have known that polyols, in addition to sucrose and trehalose, shared common properties (that is, their glass forming capacity) as stabilizing agents. Accordingly, Applicant respectfully submits that the claims are definite with respect to the nature and identity of the recited stabilizing agents.

With regard to the initial concentration of stabilizing agent, the instant specification teaches that "the stabilizing polyol enables the active agent to be stored without substantial loss of activity by denaturation, aggregation or other means." Thus, it is clear that the stabilizing agent should be present at an initial concentration that permits drying without denaturation, aggregation, or other occurrences that might result in substantial loss of activity by the active agent. As stated above, the beneficial properties of polyol stabilizing agents derive from their glass forming capacity. One of skill in the art would readily appreciate that the initial concentration of the stabilizing agent be selected so that during the drying process a supersaturated glass forming solution is formed. While it would be well within the skill of one of ordinary skill in the art to determine all of the various concentrations and combinations of stabilizing agents that produce glass forming supersaturated solutions under the claimed drying conditions, the specification provides exemplary as well as preferred ranges of stabilizing agent concentration. For example, page 7, lines 20-27, provides exemplary ranges from which the initial concentration of stabilizing agent can be selected. The Examples provide methods as well as exemplary concentration/stabilizing agent regimes that retain activity of the active agent. In Example 2 (pages 29-30), preservation samples containing concentrations of sucrose from 5% to 25% were dried without boiling or freezing to form a highly viscous liquid. One of ordinary skill in the art could (if desired) easily determine concentrations outside this range yield comparable glass forming and activity preserving results. Thus, Applicant respectfully submits that the claims are definite with respect to

the nature and concentration (%) of stabilizing agent used in the claimed compositions and methods to obtain a highly viscous liquid.

In conclusion, for at least the reasons discussed above, claims 1-39 are definite as required under 35 U.S.C. § 112, 2nd paragraph. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 112, 2nd paragraph.

Double Patenting

Claims 23-33 and 36-39 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being allegedly unpatentable over claims 1-3, 6, 14, 15-18, and 20 of copending Application No. 10/533,464. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Applicant respectfully requests deferral of the issue of double patenting until such time that the claims in this application or the claims in copending Application No. 10/533,464 are found to be otherwise allowable.

Claim Rejections – 35 U.S.C. § 102

Claims 23, 27, 28, 29, 31, 35, 36 and 39 stand rejected under 35 U.S.C. 102(b) allegedly as being anticipated by Higuchi (U.S. Patent No. 3,929,132). Applicant traverses this rejection to the the extent that the rejection is maintained with respect to the instantly amended claims.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Claim 23, and claims dependent therefrom, are directed to "a composition comprising a highly viscous liquid comprising an active agent and a glass forming polyol stabilizing agent, wherein the composition comprises a solvent content of less than 15% (w/w). Higuchi simply does not teach each and every element set forth in amended claim 23 (or the claims dependent therefrom). Higuchi relates to compositions that include up to 80% active agent with additional components, such as surfactants and/or anti-oxidants in amounts less that about 2% of the weight of the total mixture. Higuchi also discloses that

an inert solid, such as fumed silica, bentonite, *etc.* can be added in compositions having a low concentration of active agent. None of the disclosed inert solids is a glass forming polyol stabilizing agent. Nor does Higuchi teach that the disclosed inert solids have any beneficial effect with respect to preventing denaturation, aggregation and/or other means that result in loss of activity of the active agent. Rather, Higuchi states that the inert particulate solids are added to enhance the stability of the product by "providing a high solids content...to prevent the formulation from settling out upon prolonged storage." Thus, Applicant submits that Higuchi cannot reasonably be interpreted as disclosing a composition containing an active agent, which also includes a glass forming polyol stabilizing agent and has a solvent concentration of less than 15% (w/w). Accordingly, Higuchi does not anticipate claims 23, 27, 28, 29, 31, 35, 36 and 39 as amended. Applicant respectfully requests withdrawal of this rejection under 35 U.S.C. § 102.

Conclusion

On the basis of the amendments and remarks above, Applicant believes that the claims are now in condition for allowance. In the event that any substantive issues remain, Applicant hereby requests a telephonic interview with the Examiner prior to preparation of any additional written action. Accordingly, the Examiner is invited to contact the undersigned to arrange for an Examiner's interview, or to discuss the status of this application.

Respectfully submitted,

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